REMARKS

Claims 1, 3, 5-9, 12-15, 17 and 19 are now pending in the application. Claims 1 and 15 are amended herein. Support for the amendments can be found throughout the specification, for example, on page 2, paragraph [0005] and page 11, paragraph [0030]. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

EXAMINER'S INTERVIEW

Applicant acknowledges and appreciates the courtesy afforded by Examiners Fernandez and Lankford in an interview conducted on September 3, 2009 with Applicant's representative Fernando Alberdi. Applicant thanks the Examiners for recognizing, in the interview, the possibility of overcoming the references of record by amending the claims to exclude cells other than endothelial cells as the target of PEMF treatment. Applicant is filing this Amendment to reflect the input from the Examiners. Applicant has amended the claims to further define that the cell culture produced is an endothelial cell tissue culture, and the tissue culture medium produced by the endothelial cells enhances proliferation of endothelial cells and stimulates angiogenesis at said site of the bone or cartilage tissue defect, as discussed during the interview.

REJECTION UNDER 35 U.S.C. § 112

Claims 1, 3, 5, 15 and 19 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The claims are alleged to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed,

had possession of the claimed invention. The Office Action generally asserts that the recitation of the phrases "inducing cell proliferation of endothelial cells" and "enhancing said bone or cartilage tissue defect" is considered new matter. Without acquiescing with the present rejection, Applicant has amended Claim 1 to recite: "(d) administering said tissue culture medium to the site of said bone or cartilage tissue defect, wherein said administered tissue culture medium enhances proliferation of endothelial cells and stimulates angiogenesis at said site of the bone or cartilage tissue defect and thereby treating said bone or cartilage tissue defect."

Applicant respectfully submits that the claims as amended, in particular Claims 1 and 15, are fully supported by the specification and do not contain new matter. For example, Example 3 on page 11, paragraph [0030] recites the measurement of endothelial cell (HUVECs) proliferation using tissue culture media from HUVEC cells treated with PEMF. As stated in Example 3, PEMF treated culture media "demonstrates an enhancement in cell proliferation." Angiogenesis is specifically recited in an embodiment of the method, for example on page 4, paragraph [0011], which states "In one embodiment, the methods of this invention are for therapeutic angiogenesis of a human or animal subject." Treating a bone or cartilage defect has support in paragraph [0011] on the top of page 5. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 1, 3, 5, 12 and 15 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Office Action alleges that the recitation "enhancing said bone or cartilage tissue defect" is unclear. As Applicant's representative discussed with the Examiners during the Examiner Interview, this phrase refers to improvement of the defect, i.e. imparting treatment to the defect, not making the defect medically worse. Applicant has clarified

the claims by reciting that the bone and cartilage defect is treated. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

REJECTION UNDER 35 U.S.C. § 103

Claims 1, 3, 5, 9, 12, 14, 15 and 19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent. No. 6,372,494, Naughton et al., issued April 16, 2002 (hereinafter referred to as *"Naughton"*) in view of U.S. Patent No. 5,195,940, Baylink, issued March 23, 1993 (hereinafter referred to as *"Baylink"*) and/or U.S. Patent No. 6,334,069, George et al., issued December 25, 2001 (hereinafter referred to as *"George"*) and further in view of the Yen-Patton et al. reference, Journal of Cellular Physiology. 1988. 134:37-46 (hereinafter referred to as *"Yen-Patton"*).

Naughton is alleged to teach the use of conditioned cell medium from stromal cells, which include endothelial cells. (See Office Action at page 4). The conditioned medium contains growth factors and the cell conditioned medium can be used to treat, repair or regenerate tissue defects. The conditioned medium is alleged to also be used to stimulate angiogenesis and induce cell proliferation because the conditioned medium comprises angiogenic growth factors such as vascular endothelial growth factor (VEGF) and other cell growth factors. (See Office Action at page 5)

Nevertheless, *Naughton* is acknowledged as differing from the present application in that *Naughton* fails to disclose the use of pulsed electromagnetic fields (PEMF) to prepare the cell culture medium. To remedy this deficiency in *Naughton,* the Office Action alleges that *Baylink* and/or *George* teach the production of growth factor from living tissue including in vitro cell cultures using PEMF. (See Office Action at page 6). The Office Action alleges that it would

have been obvious to one of ordinary skill to have applied PEMF to a tissue culture during incubation and prior to the extraction of the conditioned medium while performing the *Naughton* invention. (See Office Action at page 7). In support of the above obviousness allegation, the Office Action alleges that "[O]ne of ordinary skill in the art would have been motivated to do this since application of an electromagnetic field would have increased growth factor production, thus resulting in a conditioned medium with a higher concentration of growth factors"

The Office Action also recognizes that *Naughton* and *Baylink* and/or *George* fail to teach application of PEMF for at least 8 hours. Here, the Office Action supplements the at least 8 hours limitation by referring to *Yen-Patton*. *Yen-Patton* is drawn to studying the effects of PEMF on a wounded vascular model using Human Umbilical Vein Endothelial Cells (HUVECS) and Bovine Aortic Endothelial Cells (BAEC). PEMF was applied to monolayers of endothelial cells for a period of time ranging from 1 hour to at least 24 hours.

To establish a *prima facie* case of obviousness, the combined prior art references must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). For the Examiner to infer that the missing features are present, there must be some apparent reason either in the references or the general knowledge in the art by which to modify the references to include the missing subject matter. See *Id.* and *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-41, 82 USPQ2d 1385, 1396 (2007). However, in the present case, the Examiner is picking and choosing features from the references of record and combining them based on "what is known in the art" without a substantiated apparent reason for their individual selection or the combination.

The references of record fail to teach or suggest a causal nexus between exposing a culture of endothelial cells to PEMF and producing a tissue culture medium capable of

proliferating endothelial cells *in vivo*. None of the references alone or reasonably combined expressly or inherently disclose administering a tissue culture medium which enhances proliferation of endothelial cells and stimulates angiogenesis at said site of the bone or cartilage tissue defect and thereby treating said bone or cartilage tissue defect.

In *Naughton*, the constructs used to produce the conditioned media are preferably made by a three-dimensional tissue construct (*Naughton* at col. 4, lines 53-54). The three dimensional stromal tissue can support the growth of tissue-specific cells later inoculated to form the three dimensional cell cultures. (*Naughton* at col. 6, lines 56-58). Stromal cells can include endothelial cells. However, the use of such co-cultures only confounds an understanding of what, if any, growth factors are produced. Moreover, there is no support that such co-cultures are even capable of producing growth factors when the co-cultures are exposed to PEMF. And even assuming, *arguendo,* that growth factors are produced, there is no support for whether they are capable of proliferating endothelial cells.

Reliance on *Baylink* and/or *George* to produce the correct growth factors in the amount necessary to enhance proliferation of endothelial cells as specifically claimed is also misplaced. *Baylink* and *George* disclose cell proliferation of cells other than endothelial cells, i.e. human osteosarcoma cells (TE-85) and Rat-2 immortalized and SA-1 human primary fibroblasts. Neither *Baylink* nor *George* teach or suggest administering a tissue culture medium which enhances proliferation of endothelial cells and stimulates angiogenesis at the site of the bone or cartilage tissue defect and thereby treating said bone or cartilage tissue defect.

Yen-Patton teaches that PEMF can be used to induce angiogenic processes in endothelial cells. But *Yen-Patton* fails to teach using the medium conditioned by endothelial cells as a repository of cell proliferative factors to induce endothelial cell growth in vivo at a defect site.

Yen-Patton teaches that there was no significant difference in cell proliferation between monolayers exposed to the field as compared to monolayers not exposed to the field. (See Table 1 in *Yen Patton*) *Yen-Patton* also fails to disclose increased production of growth factors by endothelial cells (capable of endothelial cell proliferation) when cultured in the presence of PEMF. In fact, *Yen-Patton* teaches away from the presently amended Claims 1 and 15, because one of ordinary skill would have concluded that PEMF does not have an effect on endothelial cell proliferation. (See *Yen-Patton* at page 39, footnote 1 on the bottom of Column 2, stating "No significant difference between confluent monolayers exposed to the field when compared to confluent monolayers not exposed to the field was observed").

The Office Action assumes, liberally and without supporting evidence, that applying PEMF to the co-cultures in *Naughton* would have resulted in a tissue culture media that is capable of enhancing proliferation of endothelial cells. None of the supporting references cited in this Office Action, or of the previous Office Action teach or suggest such an operation, and in fact, teach away from such a process step by the fact *Yen-Patton* failed to induce endothelial cell proliferation when monolayers were exposed to PEMF.

CONCLUSION

Applicant respectfully requests that the rejections under 35 U.S.C § 103(a) and 112 be reconsidered and withdrawn. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: October 8, 2009

By: _____
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